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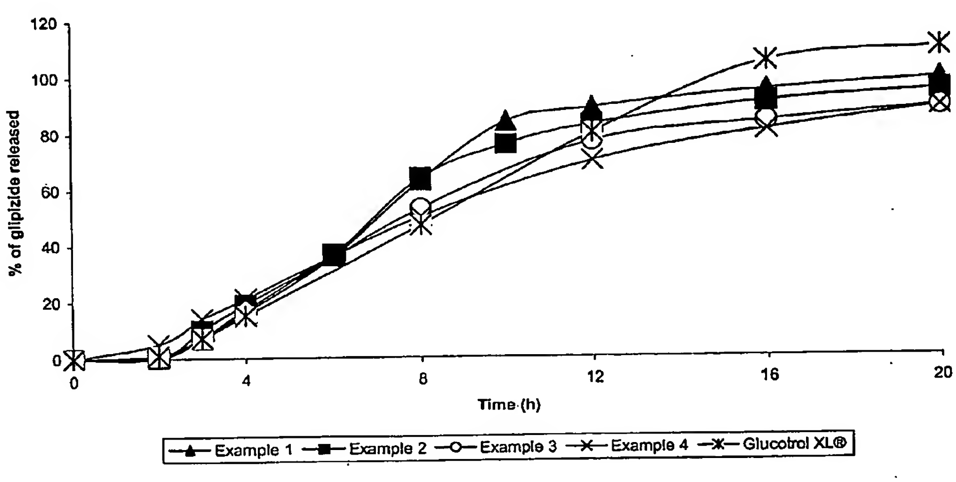
(54) Title: BIPHASIC RELEASE OF GLIPIZIDE FROM MONOCOMPARTMENT OSMOTIC DOSAGE FORM



(57) Abstract: The present invention relates to a monocompartment osmotic controlled delivery system of glipizide, providing a biphasic release of glipizide.

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BIPHASIC RELEASE OF GLIPIZIDE FROM MONOCOMPARTMENT OSMOTIC DOSAGE FORM

Field of the Invention

The present invention relates to a monocompartment osmotic controlled delivery system of glipizide, providing a biphasic release of glipizide.

Background of the Invention

Advantages of controlled release drug delivery systems are well documented. Numerous technologies have been exploited to achieve desired drug release profiles, as required to satisfy therapeutic needs and patient compliance. One such widely used controlled release technology is based on osmotic pressure controlled drug delivery, introduced by F. Theewas in *J. Pharm. Sci.*, Vol. 64, 12, 1987-91 (1975). The elementary oral osmotic system (OROS®, Alza Corp.) takes the form of a conventional coated tablet. It comprises a homogenous core tablet of drug coated with a semi-permeable wall/layer and an aperture created through the wall for the release of contents from the core. When placed in dissolution media/gastrointestinal fluid, water permeates into the core through the semipermeable wall and dissolves the drug. The osmotic pressure thus built, exerts pressure against the wall and thereby releases the solution of drug, through the aperture in the wall.

Osmotic controlled drug delivery systems show better *in vitro-in vivo* correlation as their performance is reported to be independent of pH and contents of the gastrointestinal tract. Moreover, they can be resistant to mechanical stress encountered within the gut.

Unfortunately, the use of simple osmotic systems is confined to a limited number of drugs which are soluble enough to produce a sufficiently high osmotic pressure. Sparingly soluble drugs fail to be delivered from this system in the desired manner, and therefore demand skillful modifications to exploit the advantages of these osmotic delivery systems.

U.S. Patent No. 4,111,202 assigned to Alza Corp. describes a "push-pull" (double compartment core) osmotic system, wherein the core of the OROS® system is replaced by

a pull compartment containing a sparingly soluble drug composition and a push compartment containing water soluble osmotically active agents. The two compartments are separated by means of an elastic diaphragm. When in operation, the osmotic pressure that builds up in the push compartment causes an increase in its volume. This increase in volume expands the elastic diaphragm, which thereby forces the drug out of the pull compartment through an aperture. The manufacture of "push-pull" systems is technically complicated and costly, requiring proper placement of elastic diaphragm between the two compartments. Further, for sparingly soluble drugs having large therapeutic doses, unacceptably large sized "push-pull" systems are needed.

European Patent Application No. 52917 describes osmotic systems without the elastic diaphragm. The osmotic system disclosed in this patent application has the two compartments of the push pull system replaced by two different composition layers, viz., drug layer containing drug and osmotic agents, and an expandable driving member layer formed of a water swellable hydrogel that absorbs fluid imbibed into the compartment and expands from a rested to an expanded state. The expansion of the driving member exerts pressure on the drug layer forcing its content out of the aperture. Manufacturing of the above system requires multiple compression steps and a high level of uniformity in the grain size of granulate during compression. Identification of drug layer surface for drilling of aperture through the semipermeable wall is also cumbersome.

U.S. Patent No. 4,857,336 reissued as RE 34990 and U.S. Patent No. 4,992,278, both describe homogeneous monocompartment osmotic systems. U.S. Patent No. 4,992,278 discloses a monocompartment therapeutic system comprising (a) a casing made of a material that is permeable to water and is impermeable to the components of the core containing the active ingredient, (b) a core containing an active ingredient that is sparingly soluble in water or a mixture of such active ingredients, a hydrophilic polymeric swelling agent consisting of a mixture of a vinylpyrrolidone / vinyl acetate copolymer with an ethylene oxide homopolymer, optionally water soluble substance for inducing osmosis and optionally further pharmaceutically acceptable adjuncts and (c) passage through the casing (a) for the transport of the constituents contained in the core into the surrounding aqueous body fluid. Further, this patent teaches that the use of conventional swelling agents of two-compartment system such as polyvinylpyrrolidone, polyethylene oxide, polymethacrylate and the like, in single compartment system does not work. This is

because the swelling pressure of these polymers is so great that in contact with water the semipermeable membrane bursts and the whole system disintegrates in the stomach after a short period of time.

There is thus a need for logical selection of suitable swelling agent which enables easy fabrication of monocompartment system as well as provide controlled swelling without rupturing the semipermeable membrane. On the other hand, the swelling pressure should be sufficient enough to force the contents out of the system and achieve desired controlled drug release profiles.

Summary of the Invention

The use of at least one alginic acid derivative as swelling agent in monocompartment osmotic-controlled drug delivery systems can overcome problems associated with conventional osmotic-controlled systems and helps in achieving desired controlled drug release profiles for a poorly soluble drug. The use of a alkali metal or alkali earth metal derivative in the monocompartment osmotic controlled delivery system of glipizide helps to achieve biphasic release of drugs, for example, glipizide.

Hence, in one general aspect, there is provided a monocompartment osmotic controlled delivery system of glipizide for biphasic release, the said delivery system comprising glipizide, at least one alginic acid derivative, and at least one alkali metal or alkali earth metal derivative.

In another general aspect, there is provided a monocompartment osmotic controlled delivery system of glipizide for biphasic release, the said delivery system comprising:

(a) a core comprising

(i) glipizide,

(ii) at least one alginic acid derivative,

(iii) at least one alkali metal or alkali earth metal derivative , and

(iv) at least one pharmaceutically acceptable inert excipient;

(b) a semipermeable membrane enclosing the core; and

(c) at least one passageway in the semipermeable membrane, for delivering the contents of the core into the surrounding media.

In another general aspect, there is provided a monocompartment osmotic controlled delivery system of glipizide for biphasic release, the said delivery system comprising:

(a) a core comprising

(i) glipizide,

(ii) at least one alginic acid derivative,

(iii) at least one alkali metal or alkali earth metal derivative ,

(iv) an osmotic agent, and

(v) at least one pharmaceutically acceptable inert excipient;

(b) a semipermeable membrane enclosing the core, and

(c) at least one passageway in the semipermeable membrane, for delivering the content of the core into the surrounding media.

In another general aspect, there is provided a process for the preparation of a monocompartment osmotic controlled delivery system of glipizide for biphasic release, the said process comprising the steps of:

(a) blending glipizide, at least one alginic acid derivative, at least one alkali metal or alkali earth metal derivative , and at least one pharmaceutically acceptable inert excipient; optionally granulating the blend with a binder; and compressing the blend/granules into a compact core;

(b) enclosing the core with a solution/dispersion of the enclosing composition comprising semipermeable membrane forming polymer and other coating additives; and

(c) creating at least one passageway in the semipermeable membrane.

In another general aspect, there is provided a process for the preparation of a monocompartment osmotic controlled delivery system of glipizide for biphasic release, the said process comprising the steps of:

(a) blending glipizide, at least one alginic acid derivative, at least one alkali metal or alkali earth metal derivative , an osmotic agent and at least one pharmaceutically acceptable inert excipient; optionally granulating the blend with a binder; and compressing the blend /granules into a compact core;

(b) enclosing the core with a solution/dispersion of the enclosing composition comprising semipermeable membrane forming polymer and other coating additives; and

(c) creating at least one passageway in the semipermeable membrane.

In another general aspect, there is provided a method of achieving biphasic *in-vitro* release of glipizide from a monocompartment osmotic controlled drug delivery system comprising glipizide, at least one alginic acid derivative, and at least one alkali metal or alkali earth metal derivative.

In another general aspect, there is provided a method of achieving biphasic *in-vivo* release of glipizide from a monocompartment osmotic controlled drug delivery system comprising glipizide, at least one alginic acid derivative, and at least one alkali metal or alkali earth metal derivative.

In another general aspect, there is provided a method of achieving biphasic *in-vitro* release of glipizide from a monocompartment osmotic controlled drug delivery system comprising glipizide, at least one alginic acid derivative, and at least one alkali metal or alkali earth metal derivative; wherein the second phase of glipizide release starts between about 3 to about 12 hours.

In another general aspect, there is provided a method of achieving biphasic *in-vivo* release of glipizide from a monocompartment osmotic controlled drug delivery system comprising glipizide, at least one alginic acid derivative, and at least one alkali metal or alkali earth metal derivative; wherein the second phase of glipizide release starts between about 3 to about 12 hours.

Brief description of the drawings

Figure 1 is a graph, which compares the *in vitro* release of glipizide from monocompartment osmotic system of Examples 1-4, and commercially available Glucotrol XL® (10 mg), marketed by Pfizer.

Figure 2 is a graph, which compares the *in vivo* mean plasma concentration profiles (12 subjects) of glipizide, obtained on oral administration of monocompartment osmotic system of the present invention and commercially available Glucotrol XL® (10 mg), marketed by Pfizer.

Detailed Description of the Invention

Alginic acid derivative used as a swelling agent in the monocompartment osmotic controlled drug delivery system possess the required swelling property to form a dispersion of the poorly soluble drug of a consistency, which is easily flowable through the passageway without damaging the semipermeable membrane. Combination of above attributes is rarely found amongst conventionally used swelling agents in osmotic systems. Moreover, the amount of alginic acid derivative used in the core may be varied over a wide range. Most of the alginic acid derivatives are proved to be non-toxic to humans and other mammals on oral administration and are approved for human consumption. Further, with the use of a magnesium derivative, monocompartment osmotic controlled system may be designed to provide a biphasic release of drug. The rate of drug release may also be manipulated by controlling the thickness and nature of semipermeable membrane, i.e., with proper choice of other coating additives.

When the monocompartment osmotic controlled drug delivery system of the present invention is placed in dissolution media/gastrointestinal fluid, water permeates into the core, through the semipermeable membrane. Absorption of water causes swelling of alginic acid derivative in the core, which thereby exerts pressure against the semipermeable membrane and forces the dispersion of poorly soluble drug through the passageway, into the surrounding media. On coming out of the system, the drug in the dispersion gets dissolved in the surrounding media.

The term "biphasic release" as used herein refers to two different phases of release of glipizide from the dosage form, with or without a preceding lag time. The appearance of second phase of release may be detected with a sudden increase in the rate of release at the beginning of the second phase. This can be observed by a change in the slope of the cumulative drug release profile.

The term "swelling" as used herein refers to increase in the volume on coming in contact to water. In some cases swelling may even lead to a formation of gel like

consistency into which the poorly soluble drug is embedded in the form of dispersion. Hence, the terms "swelling" and "gelling" are used interchangeably herein.

The term "core" as used herein covers any compact composition having a defined shape such as tablet, mold, capsule and the like.

The term "poorly soluble drug" as used herein includes drugs having solubility of about 1 part in 25 or more parts of water. It also includes those drugs wherein 1 part of drug dissolves in less than 25 parts of water, but under acidic or alkaline conditions, or under the influence of other excipients the solubility is decreased up to 1 in 25 parts of water. Suitable examples of the therapeutic classes, for the purpose of present invention include antidiabetics, antineoplastic agents, antihypertensives, psychopharmacological agents, cardiovascular agents, platelet aggregation inhibitors, analgesics, antimicrobials, diuretics, spasmolytics and the like. Specific examples of poorly soluble drugs include glipizide, doxazosin, verapamil, prazosin, isradipine, cilostazol, nifedipine, nisoldipine, bendroflumethazide, chlorpropamide, hydrocortisone, ibuprofen, diclofenac, and the like, and combinations thereof. The term "drug" as used herein include free drug as well as any pharmaceutically acceptable salt thereof. The poorly soluble drug as used herein may be in a commercially available form as such; or in a processed form using techniques of comminution, micro emulsification, co-melting, spray drying, co-processing with pharmaceutically acceptable inert excipients, drug-inclusion complexation and the like.

"Alginic acid derivative" as used herein include alginic acid as well as any of its pharmaceutically acceptable derivative such as salts, esters, and the like, and mixtures thereof. Specific examples of alginic acid salts include salts of alginic acid with sodium, potassium, magnesium, calcium or ammonia. Specific alginic acid esters include propylene glycol alginate.

Alginic acid is a naturally occurring hydrophilic colloidal polysaccharide consisting mainly of residues of β-1,4-linked D-mannuronic acid and α-1,4-linked L-glucuronic acid. Depending on the species of kelp used in manufacturing, ratios of mannuronic acid to glucuronic acid content typically range from 0.4 to 0.9. Alginic acid has an average molecular weight varying from about 10,000-6,00,000 and is widely used in the pharmaceutical field as a stabilizer, thickener, gelling agent and emulsifier. It is insoluble in water but its salts form thermally irreversible gels with water, whose viscosity decreases at higher pH values. Alginic acid derivatives are marketed by ISP alginates as

white to yellowish brown filamentous, grainy, granular or powdered form under the trade names – KELACID®, ALGINIC ACID HF/D, ALGINIC ACID DC, KELTONE® LVCR, KELTONE® HVCR, MANUCOL® LKX, MANUCOL LB, MANUCOL DMF, KELCOSOL®, MANUGEL® DMB, KELCOLOID® LVF, MANUCOL ESTER ERK, Improved KELMAR®, KELTOSE ®, and many others. Based on the grade used and desired drug release profile, the amount of alginic acid derivative may vary from about 5% to about 98% by weight of the total weight of core.

One of the important factors in achieving effective hydration and thereby controlled swelling of the alginic acid derivative is proper dispersion of individual particles into the core. Poor dispersion may lead to the formation of large lumps of unhydrated alginic acid derivative and significantly extend the hydration and swelling time, producing erratic drug release profiles.

One way of achieving proper dispersion of alginic acid derivative particles is blending with an osmotic agent, which diminishes its tendency to form lumps. Further, the osmotic agent may be used to manipulate the viscosity of the dispersion of poorly soluble drug formed in the core, and also to manipulate drug release profile.

The term "osmotic agent" as used herein includes all pharmaceutically acceptable inert water soluble compounds suitable for inducing osmosis, referred to in the Pharmacoepias, or in "Hager" as well as in Remington's Pharmaceutical sciences. Examples of compounds suitable as osmotic agents include water soluble salts of inorganic acids such as magnesium chloride or magnesium sulfate, lithium chloride, sodium chloride, potassium chloride, lithium hydrogen phosphate, sodium hydrogen phosphate, potassium hydrogen phosphate, lithium dihydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate; water soluble salts of organic acids such as sodium acetate, potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate; non ionic organic compounds with high water solubility e.g. carbohydrates such as mannitol, sorbitol, arabinose, ribose, xylose, glucose, fructose, mannose, galactose, sucrose, maltose, lactose, raffinose; water-soluble amino acids such as glycine, leucine, alanine, or methionine; urea and urea derivatives; and the like and mixtures thereof. The amount of osmotic agent used in the core may be up to about 60% by weight of the total weight of core.

"Semipermeable membrane" as used herein is a membrane or coating, which allows movement of water molecules through it, but does not allow contents of the core to pass through. Semipermeable membrane comprises membrane forming polymer and other pharmaceutically acceptable coating additives. Membrane forming polymers are those, which are not metabolized in the gastrointestinal tract, i.e. are ejected unchanged from the body in feces. Membrane forming polymers include those known in the art for fabrication of semipermeable membrane and described in the literature, e.g. in U.S. Patent Nos. 3,916, 899 and 3,977,404. Examples of semipermeable membrane forming polymers include cellulose derivatives such as cellulose acetate, cellulose triacetate, agar acetate, amylose acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulphonate, cellulose acetate butyl sulphonate, cellulose acetate propionate, cellulose acetate diethylamino-acetate, cellulose acetate octate, cellulose acetate laurate, cellulose acetate p-toluenesulphonate, cellulose acetate butyrate; polymeric epoxides; copolymers of alkylene oxides and alkyl glycidyl ethers; polyglycols or polylactic acid derivatives; copolymer of acrylic acid ethyl ester and methacrylic acid methyl ester; and the like; and mixtures thereof. Alternatively a combination of cellulose acetates with different degrees of acetylation may be used as membrane forming polymer. As the degree of acetylation of cellulose acetate increases, permeability of the membrane decreases. In particular, a combination of cellulose acetates having acetyl content in the range of about 8% to about 50% may be used. Further, other coating additives may be combined with the membrane forming polymers to adjust the permeability to our choice. Controlling membrane thickness also helps to manipulate the permeability of the membrane, which may vary from about 3% to about 40% weight build up over the weight of core.

The term "passageway" as used herein covers any suitable means for releasing the contents of the core into the surrounding media. The term includes passages, apertures, bores, holes, openings and the like, created through the semipermeable membrane and forming a connection between the core and the surrounding media. The passageway may be created by mechanical drilling or laser drilling, or formed in response to the osmotic pressure acting on the drug delivery system. Based on the nature of desired drug release profile, the number and diameter of the passageway may be adjusted. However, the

diameter of the passageway should not be large enough to allow body fluids to enter the drug delivery system by the process of convection.

The term "pharmaceutically acceptable inert excipients" as used herein includes all excipients used in the art of manufacturing osmotic controlled dosage forms and described in the literature. Examples include binders, diluents, surfactants, pH modifiers, lubricants/glidants, stabilizers, plasticizers, coloring agents, and the like, and mixtures thereof.

Specific examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like, and mixtures thereof.

Specific examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like, and mixtures thereof.

Surfactants may be used to promote wetting of poorly soluble drug as well as promote hydration of alginic acid derivative and include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical compositions. These include polyethoxylated fatty acids and its derivatives, for example polyethylene glycol 400 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 –150 mono dilaurate, polyethylene glycol –20 glyceryl stearate; alcohol – oil transesterification products, for example polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example propylene glycol monocaprylate; mono and diglycerides for example glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example polyethylene glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example sodium caproate, sodium glycocholate, soy

lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like; and mixtures thereof.

The pH modifiers are substances, which help in maintaining the pH of the local environment surrounding the drug at a value favorable for suitably modifying the solubility behavior of drug and/or gelling behavior of alginic acid derivative. Specific examples of pH modifiers include meglumine, trimethanolamine, ammonia, diethanolamine, ethylenediamine, L-lysine; alkali metal derivatives like dibasic sodium phosphate, sodium ascorbate, sodium citrate, tertiary sodium phosphate, sodium hydroxide and potassium hydroxide; alkali earth metal derivatives like light magnesium oxide, heavy magnesium oxide, magnesium hydroxide, calcium hydroxide, and the like, and mixtures thereof.

Use of alkali metal or alkali earth metal derivatives in monocompartment osmotic controlled delivery systems of glipizide may help to achieve biphasic release. Specific examples of alkali metal derivatives include dibasic sodium phosphate, sodium ascorbate, sodium citrate, tertiary sodium phosphate, sodium hydroxide and potassium hydroxide; alkali earth metal derivatives include light magnesium oxide, heavy magnesium oxide, magnesium hydroxide, calcium hydroxide, and the like, and mixtures thereof.

In particular magnesium oxide or magnesium hydroxide may be used. The concentration of alkali metal or alkali earth metal derivative may vary from about 0.1% w/w to about 30% w/w of the core.

Specific examples of lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like, and mixtures thereof.

Specific examples of plasticizers include acetylated triacetin, triethylcitrate, tributylcitrate, glyceroltributyrate, monoglyceride, rape oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethyl phthalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, and the like, and mixtures thereof.

Stabilizers include antioxidants, buffers, acids, and the like, and mixtures thereof.

Coloring agents include any FDA approved colors for oral use, and mixtures thereof.

The term "coating additives" as used herein includes all conventional coating additives used in the art of coating technology and described in the literature. Examples include flux enhancers as well as those described above under pharmaceutically acceptable inert excipients.

Flux enhancers are water soluble substances, which aid in drawing water from the surrounding media and are thereby helpful in manipulating the semipermeable membrane's permeability. Specific examples include hydroxymethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, hydroxypropylcellulose, propylene glycol, polyvinylpyrrolidone, and the like, and mixtures thereof.

In one of the embodiments, the monocompartment osmotic controlled delivery system of glipizide for biphasic release may be prepared by processes known in the prior art, e.g. by comminuting, mixing, granulation, sizing, filling, molding, spraying, immersing, coating etc. The core may be prepared by blending a poorly soluble drug, at least one alginic acid derivative, at least one magnesium derivative, optionally an osmotic agent and other pharmaceutically inert excipients; optionally granulating the blend; and compressing the blend/granules in to a compact core. The core may be enclosed within a semipermeable membrane by applying the enclosing composition in the form of a solution/dispersion comprising semipermeable membrane forming polymer and coating additives. Finally a passageway may be created through the semipermeable membrane using a suitable technique.

Examples of solvents used for the purpose of granulation or for preparing solution/dispersion of the coating composition include dichloromethane, isopropyl alcohol, acetone, methanol, ethanol, water, and the like, and mixtures thereof.

Alternatively, additional coating layers may be applied over the cores either below or/and over the semipermeable membrane. The additional layers comprise coating additives and provide smooth surfaces; over which semipermeable membrane may be uniformly applied or identification marks may be printed. In addition it promotes aesthetic appeal.

In case, an immediate action is desired, the monocompartment osmotic controlled delivery system may be coated with an immediate release layer comprising the same drug as in the core or a different drug, over the semipermeable membrane.

Further, a combination of more than one drug may also be used in the core and/or in the immediate release layer.

These as well as other aspects of the present invention will become apparent from the appended specification.

The invention is further illustrated by the following examples, which is for illustrative purpose and should not be construed as limiting the scope of the invention in anyway.

Examples

I. Core composition

Ingredient	**Weight (mg) per core**			
	Ex 1	**Ex 2**	**Ex 3**	**Ex 4**
Glipizide	11	11	11	11
Polyethylene glycol 4000	11	11	-	11
Poloxamer (Lütrol F 127)	11	11	-	11
Light magnesium oxide	15	-	-	-
Magnesium hydroxide	-	15	-	-
Sodium alginate	138	138	105	130
Sorbitol	137	137	170	145
Colloidal silicon dioxide	2	2	2	2
Polyvinylpyrrolidone	15	15	15	15
Magnesium stearate	4	4	6	4

II. Precoating composition

Ingredient	**Amount/tab (mg)**	
	Ex 1	**Ex 3**
Hydroxypropyl methylcellulose	4.7	2.47
Polyethylene glycol 4000	1.2	0.62

III. Semipermeable membrane

Ingredient	Amount/tab (mg)			
	Ex 1	**Ex 2**	**Ex 3**	**Ex 4**
Cellulose acetate (32% acetyl content)	-	-	45.46	-
Cellulose acetate (39.8% acetyl content)	44.3	35.2	6.83	41.6
Hydroxypropyl methylcellulose	-	-	5.06	-
Polyethylene glycol	11.1	8.8	5.06	10.4

Procedure (Example 1, 2 and 4):

1. Glipizide, light magnesium oxide/magnesium hydroxide, sodium alginate, sorbitol and aerosil were sieved and mixed together to form a homogenous blend.
2. Polyethylene glycol, poloxamer, and polyvinyl pyrrolidone were dispersed in a mixture of isopropyl alcohol and water (75:25 w/w) to form a dispersion of 35% w/w (except for example 4 where the concentration was 43% w/w).
3. The blend of step 1 was granulated with the dispersion of step 2.
4. The wet granules were dried in a fluidized bed drier and sized through suitable sieves.
5. The dried granules were lubricated by blending with magnesium stearate and compressed into round concave shaped cores using suitable tooling.
6. Hydroxypropyl methylcellulose and polyethylene glycol of the precoating composition were dissolved in a mixture of isopropyl alcohol and dichloromethane (60:40 w/w) to prepare a 5% w/w solution.
7. Cores of step 5 (Only Example 1) were coated with the solution of step 6 in a coating pan to form a precoated core.
8. Cellulose acetate and polyethylene glycol were dissolved in a mixture of acetone and water (90:10 w/w) to prepare a 4% w/w solution.
9. Precoated cores of step 7 (only Example 1) or cores of step 5 were coated with the solution of step 8 to form the semipermeable coating; and dried in hot air oven.

10. An orifice was drilled through the semipermeable membrane of coated cores of step 9 using a 0.6 mm mechanical drill to obtain monocompartment osmotic controlled delivery system of glipizide.

Procedure (Only Example 3)

1. Glipizide, sodium alginate, sorbitol and aerosil were sieved and mixed together to form a homogenous blend.
2. Polyvinyl pyrrolidone was dissolved in isopropyl alcohol.
3. The blend of step 1 was granulated with the solution of step 2.
4. The wet granules were dried in a fluidized bed drier and sized through suitable sieves.
5. The dried granules were lubricated by blending with magnesium stearate and compressed into round concave shaped cores using suitable tooling.
6. Hydroxypropyl methylcellulose and polyethylene glycol of the precoating composition were dissolved in a mixture of isopropyl alcohol and dichloromethane (60:40 w/w).
7. Cores of step 5 were coated with the solution of step 6 in a coating pan to form a precoated core.
8. Cellulose acetate, hydroxypropyl methylcellulose and polyethylene glycol were dissolved in a mixture of dichloromethane and methanol (80:20 w/w) to prepare a 3.5% w/w solution.
9. Precoated cores of step 7 were coated with the solution of step 8 to form the semipermeable coating; and dried in hot air oven.
10. An orifice was drilled through the semipermeable membrane of coated cores of step 9 using a 0.6 mm mechanical drill to obtain monocompartment osmotic controlled delivery system of glipizide.

The *in vitro* release of glipizide from monocompartment osmotic controlled delivery system of glipizide as per Examples 1-4, and commercially available Glucotrol XL® (10 mg), from Pfizer were studied in 900 ml phosphate buffer (pH 7.5) using USP II

dissolution apparatus, at a paddle speed of 50 rpm. The results of the study are incorporated herein for reference in Figure 1.

Figure 1 reveals that there is a sudden increase in the rate of glipizide release from the composition as per Examples 1 and 2, beginning around 6 hours, indicating the biphasic release. On the other hand, compositions as per examples 3 and 4 which do not have alkali metal or alkaline earth metal derivative, and Glucotrol XL® (Example 5) released glipizide at a more or less uniform rate throughout.

In vivo performance of monocompartment osmotic controlled delivery system of glipizide prepared as per the present invention (T) was evaluated with respect to the Glucotrol XL® (10 mg) tablets (R) in healthy male volunteers. Glipizide content in the blood samples was analyzed using a validated in-house HPLC method. The mean plasma concentration *vs* time profiles are incorporated herein for reference in Figure 2.

The above results clearly indicate the biphasic release of glipizide that can be achieved with the use of an alkali metal or alkali earth metal derivative. The enhanced release rate occurring at around 6 hours helps increase drug release in the colonic region, enabling better colonic absorption. Further, by providing a biphasic release, the monocompartment osmotic controlled system may help to achieve a higher concentration of glipizide during the next meal, when it is actually desired.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text and claims can be made without departing from the spirit and scope of the invention. For example, though the working examples disclosed herein incorporable magnesium derivatives, other alkali metal or alkali earth metal derivatives may be used to produce similar results. Further, though glipizide has been used as a prototype drug, the present invention may be easily used with other poorly soluble drugs as well. Moreover, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

We claim:

1. A monocompartmental osmotic-controlled delivery system for biphasic release of glipizide, the delivery system comprising:

   (a) a core comprising

      (i) glipizide,

      (ii) at least one alginic acid derivative,

      (iii) at least one alkali metal or alkali earth metal derivative, and

      (iv) at least one pharmaceutically acceptable inert excipient;

   (b) a semipermeable membrane enclosing the core; and

   (c) at least one passageway in the semipermeable membrane, for delivering the contents of the core into the surrounding media.

2. The monocompartment osmotic controlled delivery system of claim 1, wherein the alkali metal derivative is selected from dibasic sodium phosphate, sodium ascorbate, sodium citrate, tertiary sodium phosphate, sodium hydroxide and potassium hydroxide; or the alkali earth metal derivative is selected from light magnesium oxide, heavy magnesium oxide, magnesium hydroxide, and calcium hydroxide.

3. The monocompartment osmotic controlled delivery system of claim 2, wherein the alkali earth metal derivative is magnesium hydroxide.

4. The monocompartment osmotic controlled delivery system of claim 2, wherein the alkali earth metal derivative is light magnesium oxide or heavy magnesium oxide.

5. The monocompartment osmotic controlled delivery system of claim 4, wherein the alkali earth metal derivative is light magnesium oxide.

6. The monocompartment osmotic controlled delivery system of claim 1, wherein the concentration of alkali metal or alkali earth metal derivative may vary from about 0.1% to about 30% w/w of the core.

7. The monocompartment osmotic controlled delivery system of claim 1, wherein the core further comprises an osmotic agent.

8. The monocompartment osmotic controlled delivery system of claim 1, wherein the core is coated with additional layers below and/or over the semipermeable membrane.

9. The monocompartment osmotic controlled delivery system of claim 8, wherein the additional layer is an immediate release layer of drug comprising the same drug as in the core or a different drug.

10. The monocompartment osmotic controlled delivery system of claim 1, wherein the core is selected from any compact composition having a defined shape.

11. The monocompartment osmotic controlled delivery system of claim 1, wherein the alginic acid derivative is selected from alginic acid and its pharmaceutically acceptable derivative such as salts, esters, and the like.

12. The monocompartment osmotic controlled delivery system of claim 11, wherein the alginic acid salt is selected from the group comprising salts of alginic acid with sodium, potassium, magnesium, calcium or ammonia and the like.

13. The monocompartment osmotic controlled delivery system of claim 12, wherein the salt of alginic acid is sodium alginate.

14. The monocompartment osmotic controlled delivery system of claim 11, wherein the alginic acid ester is propylene glycol alginate.

15. The monocompartment osmotic controlled delivery system of claim 1, wherein the pharmaceutically acceptable inert excipient is selected from binders, diluents, surfactants, lubricants/glidants, stabilizers, plasticizers, and coloring agents.

16. The monocompartment osmotic controlled delivery system of claim 1, wherein the semipermeable membrane comprises semipermeable membrane-forming polymer and coating additives.

17. The monocompartment osmotic controlled delivery system of claim 16, wherein the semipermeable membrane-forming polymer is selected from cellulose derivatives such as cellulose acetate, cellulose triacetate, agar acetate, amylose acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate

chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulphonate, cellulose acetate butyl sulphonate, cellulose acetate propionate, cellulose acetate diethylamino-acetate, cellulose acetate octate, cellulose acetate laurate, cellulose acetate p-toluenesulphonate, cellulose acetate butyrate; polymeric epoxides; copolymers of alkylene oxides and alkyl glycidyl ethers; polyglycols or polylactic acid derivatives; copolymer of acrylic acid ethyl ester and methacrylic acid methyl ester; and the like.

18. The monocompartment osmotic controlled delivery system of claim 17, wherein the cellulose derivative is cellulose acetate.

19. The monocompartment osmotic controlled delivery system of claim 16, wherein the coating additives are selected from flux enhancers and pharmaceutically acceptable inert excipients.

20. The monocompartment osmotic controlled delivery system of claim 19, wherein the flux enhancer is selected from the group consisting of hydroxymethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, hydroxypropylcellulose, propylene glycol, polyvinylpyrrolidone and the like.

21. The monocompartment osmotic controlled delivery system of claim 20, wherein the flux enhancer is polyethylene glycol.

22. The monocompartment osmotic controlled drug delivery system of claim 7, wherein the osmotic agent is selected from water soluble salts of inorganic acids such as magnesium chloride, magnesium sulfate, lithium chloride, sodium chloride, potassium chloride, lithium hydrogen phosphate, sodium hydrogen phosphate, potassium hydrogen phosphate, lithium dihydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate; water soluble salts of organic acids such as sodium acetate, potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate; non ionic organic compounds with high water solubility, such as carbohydrates such as mannitol, sorbitol, arabinose, ribose, xylose, glucose, fructose, mannose, galactose, sucrose, maltose, lactose, raffinose; water-soluble amino acids such as glycine, leucine, alanine, or methionine; urea and urea derivatives.

23. The monocompartment osmotic controlled drug delivery system of claim 22, wherein the osmotic agent is sorbitol.

24. A process for the preparation of a monocompartment osmotic controlled drug delivery system comprising steps of:

    (a) blending a poorly soluble drug, at least one alginic acid derivative, at least one alkali metal or alkali earth metal derivative as pH modifier, and at least one pharmaceutically acceptable inert excipient to create a blend;

    (b) optionally granulating the blend with a binder;

    (c) compressing the blend /granules into a compact core;

    (d) enclosing the core with a solution / dispersion of the enclosing composition comprising semi-permeable membrane forming polymer and other coating additives; and

    (e) creating at least one passageway in the semipermeable membrane.

25. The process according to claim 24, wherein the blend of step (a) further comprises an osmotic agent.

26. The process according to claim 24, wherein the granulation or solution/dispersion of the enclosing composition is made in one or more solvent selected from dichloromethane, isopropyl alcohol, acetone, methanol, ethanol, and water.

27. A method of achieving biphasic *in-vitro/in-vivo* release of glipizide from a monocompartment osmotic controlled drug delivery system comprising glipizide, at least one alginic acid derivative, and at least one alkali metal or alkali earth metal derivative.

28. The method according to claim 27 wherein the second phase of glipizide release starts between about 3 to about 12 hours.

Fig 1

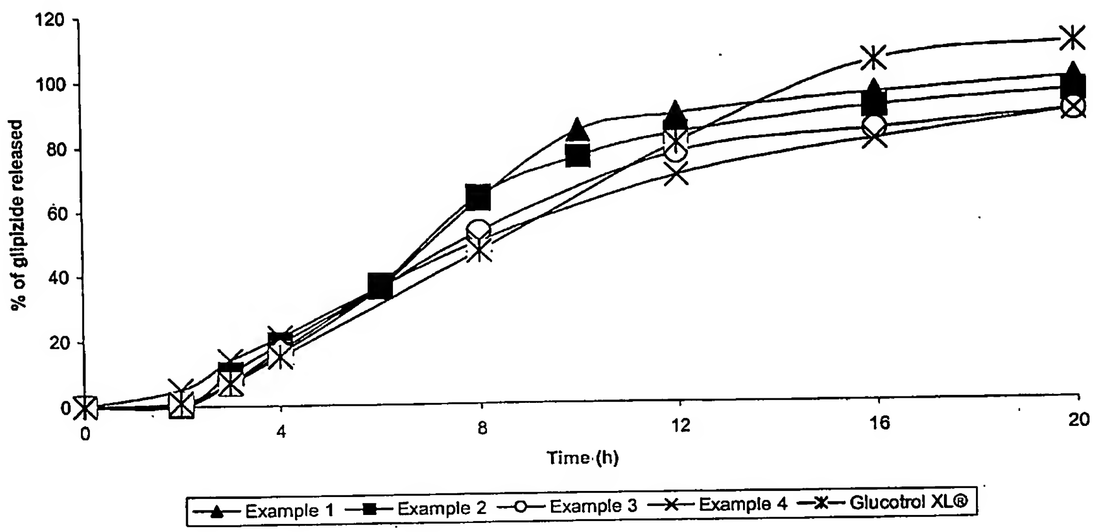
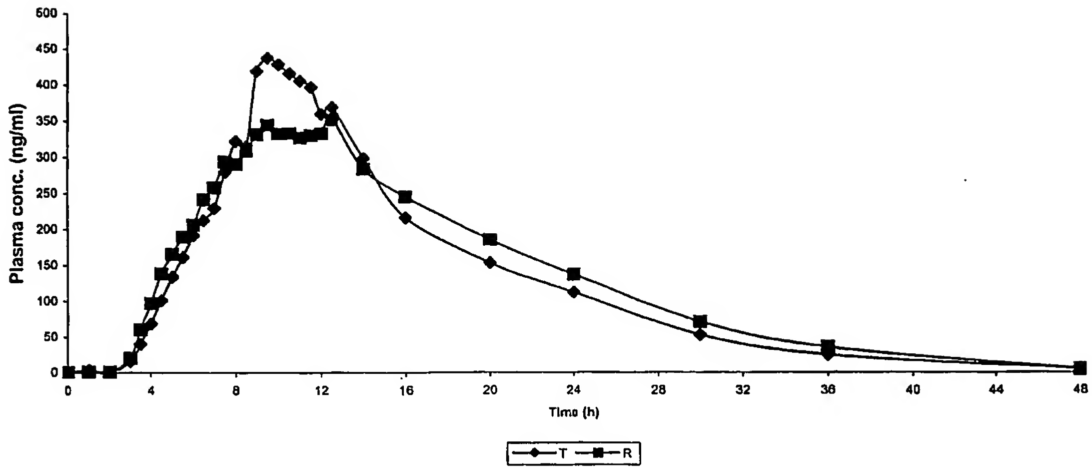

120
100
80
60
40
20
0
% of glipizide released
0
4
8
12
16
20
Time (h)
Example 1
Example 2
Example 3
Example 4
Glucotrol XL®

Fig-2


600
450
400
350
300
250
200
150
100
50
0
Plasma conc. (ng/ml)
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (h)
T
R